Human Disease Modeling Reveals Integrated Transcriptional and Epigenetic Mechanisms of NOTCH1 Haploinsufficiency.

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Public Summary:
In a team effort by three labs of Gladstone scientists, we used human induced pluripotent stem cells to discover how blood flow in the heart protects against the hardening of valves in cardiovascular disease. We show that a protein called NOTCH1, which is mutated in patients with calcific valve disease, acts in endothelial cells—cells that line the valve and vessels— to detect blood flow outside of the cell, triggering a network of gene involved in suppressing inflammation and calcification. We found that when this process is disrupted by a decrease in NOTCH1, the gene networks become disrupted and the cells activate a gene program that resembles that found in bone cells. We were able to computationally predicted genes that would be important in responding to altered NOTCH1 levels, and showed that just three genes were key modulators of the altered network in cells with lower NOTCH1 levels.

Scientific Abstract:
The mechanisms by which transcription factor haploinsufficiency alters the epigenetic and transcriptional landscape in human cells to cause disease are unknown. Here, we utilized human induced pluripotent stem cell (iPSC)-derived endothelial cells (ECs) to show that heterozygous nonsense mutations in NOTCH1 that cause aortic valve calcification disrupt the epigenetic architecture, resulting in derepression of latent pro-osteogenic and -inflammatory gene networks. Hemodynamic shear stress, which protects valves from calcification in vivo, activated anti-osteogenic and anti-inflammatory networks in NOTCH1(+/+), but not NOTCH1(+/-), iPSC-derived ECs. NOTCH1 haploinsufficiency altered H3K27ac at NOTCH1-bound enhancers, dysregulating downstream transcription of more than 1,000 genes involved in osteogenesis, inflammation, and oxidative stress. Computational predictions of the disrupted NOTCH1-dependent gene network revealed regulatory nodes that, when modulated, restored the network toward the NOTCH1(+/+) state. Our results highlight how alterations in transcription factor dosage affect gene networks leading to human disease and reveal nodes for potential therapeutic intervention.